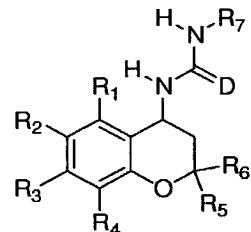


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CLAIMS

1. Benzopyran derivatives of the general formula

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(I)

wherein :

D represents S or O;

10 R₁, R₂, R₃ and R₄ are independently hydrogen, halogen, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, hydroxy, C₁₋₆-alkoxy, C₁₋₆-alkoxy-C₁₋₆-alkyl, nitro, amino, cyano, cyanomethyl, perhalomethyl, C₁₋₆-monoalkyl- or dialkylamino, sulfamoyl, C₁₋₆-alkylthio, C₁₋₆-alkylsulfonyl, C₁₋₆-alkylsulfinyl, formyl, C₁₋₆-alkylcarbonylamino, R₈arylthio, R₈arylsulfinyl, R₈arylsulfonyl, C₁₋₆-alkoxycarbonyl, C₁₋₆-alkoxycarbonyl-C₁₋₆-alkyl, carbamoyl, carbamoylmethyl, C₁₋₆-monoalkyl- or dialkylaminocarbonyl, C₁₋₆-monoalkyl- or dialkylaminothiocarbonyl, ureido, C₁₋₆-monoalkyl- or dialkylaminocarbonylamino, thioureido, C₁₋₆-monoalkyl- or dialkylaminothiocarbonylamino, C₁₋₆-monoalkyl- or dialkylaminosulfonyl, carboxy, carboxy-C₁₋₆-alkyl, acyl, R₈aryl, R₈aryl-C₁₋₆-alkyl, R₈aryloxy;

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R₅ and R₆ are each independently hydrogen, C₁₋₆-alkyl or, R₅ and R₆ taken together with the carbon atom to which they are attached form a 3- to 6-membered carbocyclic ring;

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R₇ is 2-, 3- or 4-pyridyl optionally mono- or polysubstituted by R₁ or
R₇ is 2- or 3-thienyl optionally mono- or polysubstituted substituted by R₁ or
R₇ is phenyl mono- or polysubstituted by R₁ with the exception of R₇ representing C₆H₅;

5

R₈ is hydrogen, halogen, C₁₋₆-alkyl, C₃₋₈-cycloalkyl, hydroxy, C₁₋₆-alkoxy, nitro, amino, cyano, cyanomethyl, perhalomethyl;

10 or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture or any polymorphic and tautomeric form.

2. A benzopyran derivative according to claim 1 wherein D represents S.

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3. A benzopyran derivative according to claim 1 or 2 selected from :

R/S-4-(3-Chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2H-1-benzopyran,

R/S-6-Chloro-4-(3-chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran,

R/S-4-(4-Chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2H-1-benzopyran,

R/S-6-Chloro-4-(4-chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran,

25 R/S-6-Bromo-4-(4-chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran,

R/S-4-(3-Cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2H-1-benzopyran,

R/S-6-Chloro-4-(3-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-

30 dimethyl-2H-1-benzopyran,

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- R/S-6-Bromo-4-(3-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
R/S-4-(4-Cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran,
5 R/S-6-Chloro-4-(4-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
R/S-6-Bromo-4-(4-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
R/S-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(3-nitrophenylaminothiocarbonylamino)-2*H*-1-benzopyran,
10 R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(3-nitrophenylaminothiocarbonylamino)-2*H*-1-benzopyran,
R/S-3,4-Dihydro-2,2-dimethyl-6-fluoro-4-(4-nitrophenylaminothiocarbonylamino)-2*H*-1-benzopyran,
15 R/S-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(4-nitrophenylaminothiocarbonylamino)-2*H*-1-benzopyran,
R/S-4-(3-Chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran,
R/S-6-Chloro-4-(3-chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
20 R/S-4-(4-Chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran,
R/S-6-Chloro-4-(4-chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
25 R/S-6-Bromo-4-(4-chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
R/S-4-(3-Cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran,
R/S-6-Chloro-4-(3-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
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- R/S-6-Bromo-4-(3-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
R/S-4-(4-Cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran,
5 R/S-6-Chloro-4-(4-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
R/S-6-Bromo-4-(4-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
R/S-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(3-nitrophenylaminothiocarbonylamino)-2*H*-1-benzopyran,
10 R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(3-nitrophenylaminothiocarbonylamino)-2*H*-1-benzopyran,
R/S-3,4-Dihydro-2,2-dimethyl-6-fluoro-4-(4-nitrophenylaminothiocarbonylamino)-2*H*-1-benzopyran,
R/S-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(4-nitrophenylaminothiocarbonylamino)-2*H*-1-benzopyran,
15 R/S-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(4-nitrophenylaminothiocarbonylamino)-2*H*-1-benzopyran,
R/S-4-(3-Chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran,
R/S-6-Chloro-4-(3-chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
20 R/S-4-(4-Chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran,
R/S-6-Chloro-4-(4-chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
R/S-6-Bromo-4-(4-chlorophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
25 R/S-4-(3-Cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran,
R/S-6-Chloro-4-(3-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
30 R/S-6-Chloro-4-(3-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,

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- R/S-6-Bromo-4-(3-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran,
R/S-4-(4-Cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2H-1-benzopyran,
5 R/S-6-Chloro-4-(4-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran,
R/S-6-Bromo-4-(4-cyanophenylaminothiocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran,
R/S-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(3-nitrophenylaminothiocarbonylamino)-2H-1-benzopyran,
10 R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(3-nitrophenylaminothiocarbonylamino)-2H-1-benzopyran,
R/S-3,4-Dihydro-2,2-dimethyl-6-fluoro-4-(4-nitrophenylaminothiocarbonylamino)-2H-1-benzopyran,
R/S-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(4-nitrophenylaminothiocarbonylamino)-2H-1-benzopyran,
15 R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(4-nitrophenylaminothiocarbonylamino)-2H-1-benzopyran,
R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(4-nitrophenylaminothiocarbonylamino)-2H-1-benzopyran,
R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(4-nitrophenylaminothiocarbonylamino)-2H-1-benzopyran,
20 R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(4-nitrophenylaminothiocarbonylamino)-2H-1-benzopyran,
R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(3-trifluoromethylphenylaminothiocarbonylamino)-2H-1-benzopyran,
R/S-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-methoxyphenylaminocarbonylamino)-2H-1-benzopyran,
25 R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(2-methoxyphenylaminocarbonylamino)-2H-1-benzopyran,
R/S-3,4-Dihydro-2,2-dimethyl-6-fluoro-4-(3-methoxyphenylaminocarbonylamino)-2H-1-benzopyran,
R/S-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(3-methoxyphenylaminocarbonylamino)-2H-1-benzopyran,
30 R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(3-methoxyphenylaminocarbonylamino)-2H-1-benzopyran,

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- R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(3-methoxyphenylaminocarbonylamino)-2*H*-1-benzopyran,
R/S-3,4-Dihydro-2,2-dimethyl-6-fluoro-4-(4-methoxyphenylaminocarbonylamino)-2*H*-1-benzopyran,
5 R/S-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(4-methoxyphenylaminocarbonylamino)-2*H*-1-benzopyran,
R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(4-methoxyphenylaminocarbonylamino)-2*H*-1-benzopyran,
R/S-3,4-Dihydro-2,2-dimethyl-6-fluoro-4-(2-methylphenylaminocarbonylamino)-2*H*-1-benzopyran,
10 R/S-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-methylphenylaminocarbonylamino)-2*H*-1-benzopyran,
R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(2-methylphenylaminocarbonylamino)-2*H*-1-benzopyran,
15 R/S-3,4-Dihydro-2,2-dimethyl-6-fluoro-4-(3-methylphenylaminocarbonylamino)-2*H*-1-benzopyran,
R/S-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(3-methylphenylaminocarbonylamino)-2*H*-1-benzopyran,
R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(3-methylphenylaminocarbonylamino)-2*H*-1-benzopyran,
20 R/S-3,4-Dihydro-2,2-dimethyl-6-fluoro-4-(3-methylphenylaminocarbonylamino)-2*H*-1-benzopyran,
R/S-3,4-Dihydro-2,2-dimethyl-6-fluoro-4-(4-methylphenylaminocarbonylamino)-2*H*-1-benzopyran,
R/S-6-Chloro-3,4-dihydro-2,2-dimethyl-4-(4-methylphenylaminocarbonylamino)-2*H*-1-benzopyran,
25 R/S-6-Bromo-3,4-dihydro-2,2-dimethyl-4-(4-methylphenylaminocarbonylamino)-2*H*-1-benzopyran,
R/S-4-(2-Chlorophenylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2*H*-1-benzopyran,
R/S-6-Chloro-4-(2-chlorophenylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran,
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- R/S-6-Bromo-4-(2-chlorophenylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran,
R/S-4-(3-Chlorophenylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2H-1-benzopyran,
5 R/S-6-Chloro-4-(3-chlorophenylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran,
R/S-6-Bromo-4-(3-chlorophenylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran,
R/S-4-(4-Chlorophenylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-6-fluoro-2H-1-benzopyran,
10 R/S-6-Chloro-4-(4-chlorophenylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran,
R/S-6-Bromo-4-(4-chlorophenylaminocarbonylamino)-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran.
15
4. Benzopyran derivatives according to any one of the preceding claims for use as openers of the K_{ATP}-regulated potassium channels.
5. A pharmaceutical composition comprising a benzopyran derivative according
20 to any one of the preceding claims or pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base or any optical isomer or mixture of optical isomers, including a recemic mixture or any tautomeric form together with one or more pharmaceutically acceptable carriers of diluents.
25 6. A pharmaceutical composition for use in the treatment of diseases of the endocrinological system such as hyperinsulinaemia and diabetes comprising a benzopyran derivative according to any one of the preceding benzopyran derivative claims or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of

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optical isomers, including a racemic mixture, or any tautomeric form together with a pharmaceutically acceptable carrier or diluent.

7. The pharmaceutical composition according to any one of the claims 5 or 6 in
5 the form of an oral dosage unit or parental dosage unit.

8. A pharmaceutical composition according to any one of the claims 5 or 6
wherein said benzopyran derivative is administered as a dose in a range from
about 0.05 to 1000, preferably from about 0.1 to 500 and especially in the range
10 from 50 to 200 mg per day.

9. A benzopyran derivative according to any one of the preceding benzopyran
derivative claims or a pharmaceutically acceptable salt thereof with a
pharmaceutically acceptable acid or base, or any optical isomer or mixture of
15 optical isomers, including a racemic mixture, or any tautomeric form for
therapeutical use.

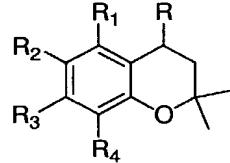
10. A benzopyran derivative according to any one of the preceding benzopyran
derivative claims or a pharmaceutically acceptable salt thereof with a
pharmaceutically acceptable acid or base, or any optical isomer or mixture of
20 optical isomers, including a racemic mixture, or any tautomeric form for
therapeutical use in then treatment of diseases of the endocrinological system,
such as hyperinsulinaemia and diabetes.

25 11. The use of a benzopyran derivative according to any one of the preceding
compound claims or a pharmaceutically acceptable salt thereof with a
pharmaceutically acceptable acid or base, or any optical isomer or mixture of
optical isomers, including a racemic mixture, or any tautomeric form as a
medicament.

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12. The use of a benzopyran derivative according to any of the preceding compound claims for preparing a medicament.
13. The use of a benzopyran derivative according to any one of the preceding 5 benzopyran derivative claims or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment of diseases of the endocrinological system, such as hyperinsulinaemia and diabetes.
14. A method of treating diseases of the endocrinological system, such as hyperinsulinaemia and diabetes in a subject in need thereof comprising administering an effective amount of a benzopyran derivative according to any 10 one of the preceding benzopyran derivative claims to said subject.
15. A process for the manufacture of a medicament, particular to be used in the treatment of diseases of the endocrinological system, such as hyperinsulinaemia and diabetes which process comprising bringing a compound of formula (I) according to any one of the preceding compound claims 1 or a pharmaceutically 15 acceptable salt thereof into a galenic dosage form.
16. A method of preparing a benzopyran derivative of formula (I) which comprises :
- reacting a compound of formula (II)

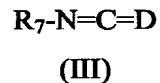
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(II)

wherein R represents NH₂ and R₁, R₂, R₃ and R₄ are defined as for formula (I) with an isothiocyanante of formula (III)

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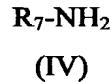


wherein D represents S or O and R₇ is defined as for formula (I), to form a benzopyran derivative of formula (I); or

10

- reacting a compound of formula (II) wherein R represents -N=C=S and R₁, R₂, R₃ and R₄ are defined as for formula (I) with an amine of formula (IV)

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wherein R₇ is defined as for formula (I), to form a benzopyran derivative of formula (I).